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Title of Document: **DECLARATION (originally filed July 20, 2007, missing 2 pages) (complete declaration attached)**

Applicant: SHIMIZU ET AL.
Serial No.: 09/403429
App. Filed: October 20, 1999
Group Art No.: 1615
Conf. No.: 7265

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August 22, 2007
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
Toshihiro SHIMIZU et al.	:	
Serial No. 09/403,429	:	Group Art Unit 1615
Filed on October 20, 1999	:	Examiner: TRAN, Susan T.

For: RAPIDLY DISINTEGRABLE SOLID PREPARATION

DECLARATION UNDER 37 CFR 1.132

Honorable Commissioner of
Patents and Trademarks,
Washington, D.C. 20231

Sirs:

I, Toshihiro SHIMIZU, declare:

That I am a citizen of Japan residing at 15-3, Aramakiminami 2-chome, Itami-shi, Hyogo, Japan;

That I was born on July 10, 1964 in Okayama, Japan;

That I graduated from Gifu Pharmaceutical University, with degree of Bachelor of Pharmaceutical Science in March 1988;

That I have been employed by Takeda Chemical Industries, Ltd. (now, Takeda Pharmaceutical Company Limited), Osaka, Japan, since April, 1988, and have been engaged in research and development in the Pharmaceutical Production Division of said company;

That I have been appointed a Research Head of Pharmaceutical Technology Research & Development Laboratories in said Pharmaceutical Production Division since 2004;

That I was awarded a Ph. D in Formulation Study of Lansoprazole Fast-disintegrating Tablets containing Enteric Coated Microgranules from Kyushu University in March, 2005;

That I am a member of the Pharmaceutical Society of Japan, and have published, with other research workers, a number of reports on scientific studies, among others, including

1. Shimizu T., Nakano T., Morimoto S., Tabata T., Hamaguchi N., Igari Y., *Chem. Pharm. Bull.*, 51, 942-947 (2003)

2. Shimizu T., Kameoka N., Iki H., Tabata T., Hamaguchi N., Igari Y., *Chem.*

Pharm. Bull., 51, 1029-1035 (2003)

3. Shimizu T., Sugaya M., Nakano Y., Izutsu D., Mizukami Y., Okochi K., Tabata T., Hamaguchi N., Igari Y., *Chem. Pharm. Bull.*, 51, 1121-1127 (2003);

That I am one of the co-inventors of the above-identified U.S. Patent Application Serial No. 09/403,429 filed on October 20, 1999;

That the following Experiments were conducted by myself and under my supervision and control:

Experiments

Experiment 1

Purpose

The tablet shown in Example 2 of Depui et al. (US 6,365,184) was reproduced, and disintegration time and oral disintegration time were measured. As L-HPC, L-HPC LH-32 (hydroxypropoxyl group content: 7.0-9.9%) was used. Based on my knowledge and experience, I consider myself to be familiar with the materials that were commercially available for pharmaceutical formulations before the priority date of the present application (July 28, 1998). I believe that the L-HPC LH32 material would correspond to the material having the lowest hydroxypropoxyl group content that was commercially available, whether from Shin-Etsu or any other source, before the priority date of the present application (July 28, 1998).

Method

Enteric coated granules were produced at the mixing ratio of the enteric coated granules of Example 2 of Depui et al. (US 6,365,184) and using lansoprazole instead of omeprazole (Preparation A).

The formulations of US 6,365,184 (Example 2) and Preparation A are shown below.

1. Production of enteric coated granules

1.1. Active compound layer

Lansoprazole, magnesium carbonate, polysorbate 80 and hydroxypropyl methylcellulose were dissolved and suspended in purified water to give a suspenstion. Using a rotating fluidized-bed granulator, Nonpareil cores (Nonpareil 101 (24-32M)) were coated by spraying the suspension.

Table 1 Formulation of core and active compound layer

	Material	US6,365,184 (g)	Preparation A (g)
Core	Nonpareil cores	150	150
Active compound layer	S-omeprazole magnesium	120	-
	Lansoprazole	-	100
	Magnesium carbonate	-	20
	Polysorbate 80	2.4	2.4
	Hydroxypropyl methylcellulose	18	18
	Purified water	562	562
	Subtotal (solid ingredients)	140.4	140.4
		702.4	702.4
	Total	290.4	290.4

1.2. Separating layer

Hydroxypropyl cellulose, talc and magnesium stearate were dissolved and suspended in purified water to give a separating layer suspension. Using a rotating fluidized-bed granulator, the core material obtained in above-mentioned 1.1 was coated by spraying the separating layer suspension and was dried.

Table 2 Formulation of separating layer

	Material	US6,365,184 (g)	Preparation A (g)
Core material	Core material	200	200
Separating layer	Hydroxypropyl cellulose	30	30
	Talc	51.4	51.4
	Magnesium stearate	4.3	4.3
	Purified water	600	600
	Subtotal (solid ingredients)	85.7	85.7
		685.7	685.7
	Total	285.7	285.7

1.3. Enteric coating layer

Polysorbate 80 was dissolved in purified water, and the mixture was heated to 70°C. Mono- and diglycerides were added, and the mixture was dispersed using a dispersing apparatus, and then cooled to room temperature. To this dispersion were added triethyl citrate and methacrylic acid copolymer 30% suspension, and they were mixed to give an enteric coating suspension.

Using a rotating fluidized-bed granulator, the pellets with separating layer obtained in above-mentioned 1.2 were coated by spraying the enteric coating suspension.

Table 3 Formulation of enteric coating

	Material	US6,365,184 (g)	Preparation A (g)
Pellets with separating layer	Pellets with separating layer	250	250
Enteric coating layer	Methacrylic acid copolymer 30% suspension (as solid ingredient)	333.7 (100.1)	333.7 (100.1)
	Triethyl citrate	30	30
	Mono-and diglycerides	5	5
	Polysorbate 80	0.5	0.5
	Purified water	195.8	195.8
	Subtotal (solid ingredients)	135.6 565	135.6 565
	Total	385.6	385.6

1.4. Over-coating layer

Carboxymethylcellulose sodium was dissolved in purified water to give an over-coating solution. Using a rotating fluidized-bed granulator, the enteric coating layered pellets obtained in above-mentioned 1.3 were coated by spraying the over-coating solution and was dried.

Table 4 Formulation of over-coating layer

	Material	US6,365,184 (g)	Preparation A (g)
Enteric coating layered pellets	Enteric coating layered pellets	371	371
Over-coating layer	Carboxymethylcellulose sodium	5	5
	Purified water	191	191
	Subtotal (solid ingredient)	5 196	5 196
	Total	376	376

2. NSAID Granules

Polyvinylpyrrolidone K-90 was dissolved in purified water to give a binding solution. Using a vertical granulator (FM-VG-10), naproxen, microcrystalline cellulose and L-HPC LH-32 were mixed. The binding solution was added and the mixture was

kneaded and dried in a shelf dryer at 60°C for 5 hr. The obtained granules were sized using a 1000 μm standard sieve.

Table 5 Formulation of NSAID Granules

Material	US6,365,184 (g)	Preparation A (g)
Naproxen	250	250
Microcrystalline cellulose	150	150
L-HPC LH-32	40	40
Polyvinylpyrrolidone K-90	5	5
Purified water	250	250
Total (solid ingredients)	445	445

3. Mixing and tableting

The over-coated pellets comprising lansoprazole and NSAID Granules were mixed 50 times in a bag. Using Shimazu universal testing machine (UH-10A) with a 11 mmϕ flat punch, the mixed powder (500 mg) was tableted at a compression force of 9 KN/punch.

Table 6 Formulation of mixed powder

Material	US6,365,184 (g)	Preparation A (g)
Over-coated pellets comprising lansoprazole	55	55
NSAID Granules	445	445
Total	500	500

4. Property of tablet

The hardness, disintegration time and oral disintegration time of the tablet were measured.

Hardness: Hardness of each of 3 tablets was measured using Tablet tester 60 (Schleuniger) and mean value was calculated.

Disintegration time: The measurement was carried out according to the disintegration test method of EP (European Pharmacopoeia) using purified water as a test solution.

Oral disintegration time: The measurement was carried out in three healthy human subjects. After the mouth was rinsed with water, one tablet was held in the mouth until the tablet disintegrated without chewing. The disintegration time was recorded.

Results

The results of the measurements are shown in Table 7. Securing the equivalent hardness as in Example 2 of Depui et al. (US 6,365,184), the disintegration time and oral disintegration time were measured. In the disintegration test according to EP, the tablet was disintegrated in 30 sec, showing rapid disintegration property. As for the oral disintegration time, however, only about half of the tablet was found to have been disintegrated after staying in the mouth for 5 min.

Table 7 Results of measurements

	Example 2 of US 6,365,184 (reported)	Preparation A
Hardness (mean)	9.4 kP	9.7 kP
Disintegration time	15-30 sec	30-30 sec
Oral disintegration time	---	The tablet was not disintegrated in 5 min, too sticky and spit out due to uncomfortable feeling.

Experiment 2

Purpose

The disintegration time and oral disintegration time of the combination of Depui et al. (US 6,365,184) and Khankari et al. (US 6,024,981) (tablet of the formulation of Example 2 of Depui added with mannitol) were measured. As L-HPC, L-HPC LH-32 (hydroxypropoxyl group content: 7.0-9.9%) having the lowest hydroxypropoxyl group content, which was commercially available before the priority date of the present application (July 28, 1998), was used.

Method

Enteric coated granules were produced at the mixing ratio of the enteric coated granules of Example 2 of Depui et al. (US 6,365,184) and using lansoprazole instead of omeprazole. Furthermore, mannitol was added as an excipient (Preparation B).

The formulations of US 6,365,184 (Example 2) and Preparation B are shown below.

1. Production of enteric coated granules
1.1. Active compound layer

Lansoprazole, magnesium carbonate, polysorbate 80 and hydroxypropyl methylcellulose were dissolved and suspended in purified water to give a suspenstion.

Using a rotating fluidized-bed granulator, Nonpareil cores (Nonpareil 101 (24-32M)) were coated by spraying the suspension.

Table 8 Formulation of core and active compound layer

	Material	US6,365,184 (g)	Preparation B (g)
Core	Nonparcil cores	150	150
Active compound layer	S-omeprazole magnesium	120	-
	Lansoprazole	-	100
	Magnesium carbonate	-	20
	Polysorbate 80	2.4	2.4
	Hydroxypropyl methylcellulose	18	18
	Purified water	562	562
	Subtotal (solid ingredients)	140.4	140.4
		702.4	702.4
	Total	290.4	290.4

1.2. Separating layer

Hydroxypropyl cellulose, talc and magnesium stearate were dissolved and suspended in purified water to give a separating layer suspension. Using a rotating fluidized-bed granulator, the core material obtained in above-mentioned 1.1 was coated by spraying the separating layer suspension and was dried.

Table 9 Formulation of separating layer

	Material	US6,365,184 (g)	Preparation B (g)
Core material	Core material	200	200
Separating layer	Hydroxypropyl cellulose	30	30
	Talc	51.4	51.4
	Magnesium stearate	4.3	4.3
	Purified water	600	600
	Subtotal (solid ingredients)	85.7	85.7
		685.7	685.7
	Total	285.7	285.7

1.3. Enteric coating layer

Polysorbate 80 was dissolved in purified water, and the mixture was heated to 70°C. Mono- and diglycerides were added, and the mixture was dispersed using a dispersing apparatus, and then cooled to room temperature. To this dispersion were added triethyl citrate and methacrylic acid copolymer 30% suspension, and they were mixed to give an enteric coating suspension.

Using a rotating fluidized-bed granulator, the pellets with separating layer obtained in above-mentioned 1.2 were coated by spraying the enteric coating suspension.

Table 10 Formulation of enteric coating layer

	Material	US6,365,184 (g)	Preparation B (g)
Pellets with separating layer	Pellets with separating layer	250	250
Enteric coating layer	Methacrylic acid copolymer 30% suspension (as solid ingredient)	333.7 (100.1)	333.7 (100.1)
	Triethyl citrate	30	30
	Mono-and diglycerides	5	5
	Polysorbate 80	0.5	0.5
	Purified water	195.8	195.8
	Subtotal (solid ingredients)	135.6 565	135.6 565
	Total	385.6	385.6

1.4. Over-coating layer

Carboxymethylcellulose sodium was dissolved in purified water to give an over-coating solution. Using a rotating fluidized-bed granulator, the enteric coating layered pellets obtained in above-mentioned 1.3 were coated by spraying the over-coating solution and was dried.

Table 11 Formulation of over-coating layer

	Material	US6,365,184 (g)	Preparation B (g)
Enteric coating layered pellets	Enteric coating layered pellets	371	371
Over-coating layer	Carboxymethylcellulose sodium	5	5
	Purified water	191	191
	Subtotal (solid ingredient)	5 196	5 196
	Total	376	376

2. NSAID Granules

Polyvinylpyrrolidone K-90 was dissolved in purified water to give a binding

solution. Using a vertical granulator (FM-VG-10), naproxen, mannitol, microcrystalline cellulose and L-HPC LH-32 were mixed. The binding solution was added and the mixture was kneaded and dried in a shelf dryer at 60°C for 5 hr. The obtained granules were sized using a 1000 μm standard sieve.

Table 12 Formulation of NSAID Granules

Material	US6,365,184 (g)	Preparation B (g)
Naproxen	250	250
Mannitol	-	300
Microcrystalline cellulose	150	150
L-HPC LH-32	40	40
Polyvinylpyrrolidone K-90	5	5
Purified water	250	250
Total (solid ingredients)	445	745

3. Mixing and tableting

The over-coated pellets comprising lansoprazole and NSAID Granules were mixed 50 times in a bag. Using Shimazu universal testing machine (UH-10A) with a 11 mmϕ flat punch, the mixed powder (500 mg) was tableted at a compression force of 9 KN/punch.

Table 13 Formulation of mixed powder

Material	US6,365,184 (g)	Preparation B (g)
Over-coated pellets comprising lansoprazole	55	55
NSAID Granules	445	445
Total	500	500

4. Property of tablet

The hardness, disintegration time and oral disintegration time of the tablet were measured.

Hardness: Hardness of each of 3 tablets was measured using Tablet tester 60 (Schleuniger) and mean value was calculated.

Disintegration time: The measurement was carried out according to the disintegration test method of EP (European Pharmacopoeia) using purified water as a test solution.

Oral disintegration time: The measurement was carried out in three healthy human subjects. After the mouth was rinsed with water, one tablet was held in the mouth until

the tablet disintegrated without chewing. The disintegration time was recorded.

Results

The results of the measurements are shown in Table 14. Securing the equivalent hardness as in Example 2 of Depui et al. (US 6,365,184), the disintegration time and oral disintegration time were measured. In the disintegration test according to EP, the tablet was disintegrated within 30 sec, showing rapid disintegration property. As for the oral disintegration time, however, the tablet was disintegrated in 246 sec, or the tablet was not disintegrated after staying in the mouth for 5 min.

Table 14 Results of measurements

	Example 2 of US 6,365,184 (reported)	Preparation B
Hardness (mean)	9.4 kP	10.3 kP
Disintegration time	15-30 sec	18-24 sec
Oral disintegration time	—	The tablet was disintegrated in 246 sec, or the tablet was not disintegrated in 5 min.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed on this 11th day of July, 2007

Toshihiro Shimizu

Toshihiro SHIMIZU